Effects of Oral L-Carnitine Supplementation on Leptin and Adiponectin Levels and Body Weight of Hemodialysis Patients

A Randomized Clinical Trial

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Original Paper

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Introduction. Carnitine supplementation may improve the general health and quality of life of hemodialysis patients by improving adipokines levels. The aim of the study was to investigate the effects of L-carnitine supplementation on leptin levels, adiponectin levels, and body weight of hemodialysis patients.

Materials and Methods. Fifty hemodialysis patients were randomly divided into the carnitine group, who received oral L-carnitine, 1 g/L for 3 months, and the control group. Anthropometric measurements and serum levels of adipokines were measured at baseline and at the end of the intervention.

Results. Forty-two participants completed the study. Serum leptin concentrations decreased after 12 weeks of the intervention in both groups, but these changes were not significant. The mean change of leptin concentration were, -1.7 ± 19.0 µg/mL and -7.1 ± 20.0 µg/mL in the carnitine group and the control group, respectively (P = .39). The mean adiponectin levels at baseline and after the intervention were 8.6 ± 11.19 µg/mL and 9.8 ± 4.1 µg/mL in the carnitine group (P = .67) and 5.0 ± 2.5 µg/mL and 11.2 ± 5.4 µg/mL in the control group, respectively (P < .001). Serum adiponectin levels increased significantly in the control group only. The decrease in body mass index was not significant.

Conclusions. This study showed that a daily supplementation of 1000 mg oral syrup of L-carnitine for 12 weeks did not affect leptin and adiponectin levels or the body weight or body mass index of hemodialysis patients.

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INTRODUCTION

The high growth rate of patients suffering from end-stage renal disease (ESRD) is becoming a threat for global community. In Iran, the incidence of ESRD has increased from 49.9 to 64.0 per million population in a 6 years' time period (2000-2006).[1] Despite achieving technological advances in the field of dialysis, the progression of metabolic disorders leads to higher mortality rates in hemodialysis patients.[2]

Serum levels of adipokines is impaired in patients with kidney failure.[3] Changes in the adipokine balance in chronic kidney disease (CKD) patients may not only cause metabolic disturbances in these patients, but also change or improve insulin resistance and inflammation.[4] Serum levels of leptin

and adiponectin rise in hemodialysis patients. This shows that the kidney is an important factor in adiponectin renal clearance.[4,5] Kwan and associates demonstrated that expression of the adiponectin gene decreases in patients with CKD.[6] Carnitine (3-hydroxi-4-N-trimethylammoniobutanoate), a short organic hydrosoluble molecule, is present in biological materials as free carnitine and acyl carnitines. Carnitine, as a pivotal molecule in human energy metabolism system, transports long-chain fatty acids across the inner mitochondrial membrane and controls the rates of long-chain fatty acids beta oxidations.[7] Only 1% of total carnitine is present in plasma and over 98% of carnitine are found in the skeletal and cardiac muscles. A small amount is also present in the kidney, liver, and brain.[8,9]

Carnitine deficiency is observed in half of female patients and one-third of male patients with ESRD that are on long-term dialysis, and their carnitine levels will continue to decrease with age.[10] Supplementation with L-carnitine has been efficient to reduce clinical disorders in ESRD patients. However, there are various studies with negative results for L-carnitine supplementation in ESRD.[11] In most cases, carnitine supplementation improves the general health and quality of life in hemodialysis patients. Furthermore, L-carnitine may positively influence the nutritional status of hemodialysis patients by promoting a positive protein balance and by reducing insulin resistance and chronic inflammation, possibly through its effect on leptin resistance. In obese women with type II diabetes mellitus and hypocaloric diet, L-carnitine supplementation reduced serum adipokines (leptin and visfatin) and inflammatory markers and anthropometric indexes, especially adiposity (abdominal fat). Considering the unknown biochemical pathway,[12] the current study was designed to investigate the effects of oral L-carnitine supplementation on serum leptin and adiponectin concentration and body weight of hemodialysis patients.

MATERIALS AND METHODS

Study Design and Participants

The present study was a randomized controlled trial performed with the participation of patients on long-term hemodialysis at Seyed-o-Shohada Hospital, Shahid Rahnamoun Hospital, and Shahid Sadooghi Hospital, in Yazd, Iran, from September 2013 to June 2014. Inclusion criteria were participants older than 20 years and on hemodialysis treatment for at least 1 year. Having an infectious, liver, thyroid, or cancer disease; receiving L-carnitine at least 8 weeks prior to the start of the study, being on corticosteroids, or participating in another research project made up the exclusion criteria.

Ethical Considerations

The goals and methods of the study were explained to patients, and an informed consent form was signed by each participant. The patients could withdraw at any time or at any stage of the research. The study protocol was approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences and was registered at www.irct.ir with the code of IRCT2013070913160N2.

Study Design

Considering a study potency of 80%, an alfa equal to 5, previous studies parameters,[13-15] and an attrition of 10% during the study, the final sample size was determined to be 50 patients. They were divided by random allocation using random numbers table into 2 the carnitine group and the control group. Patients in the carnitine group received 1000 mg of oral L-carnitine at the evening and after a hemodialysis session in the form of 20-mL L-carnitine syrup (Alborzdarou Co, Tehran, Iran) every day after dinner for 12 weeks.[13,16] Patients in the control group did not receive L-carnitine supplementation. The participants were visited monthly at the dialysis centers and supplements were delivered to them separated by the visits. To ensure of syrup consumption, the completed drug recall forms were taken from the patients.

Measurements

Demographic characteristics including age, sex, body mass index (BMI), dialysis duration, and clinical history were recorded at baseline. Patients were weighed while wearing minimal clothing at baseline and at the end of intervention using a Seca digital scale (Germany) with an accuracy of 100 g. Height without shoes was measured using a stadiometer with an accuracy of 0.05 cm. Patients' nutritional status were assessed at the beginning of the study using the Malnutrition-Inflammation Score (MIS) method. The MIS forms were completed

by a nutritionist and a physician for each patient.

The MIS form had 10 components. The first part was about the patient's related medical history and included change in end-dialysis dry weight, dietary intake, gastrointestinal symptoms, functional capacity, comorbidity, and the number of years on dialysis. The second part concerned the physical examination results (according to the Subjective Global Assessment criteria) and included decreased fat stores or loses of subcutaneous fat and signs of muscle wasting. This form also included 3 other components: BMI, serum albumin, and serum total iron-binding capacity.[17]

All biochemical tests were done at the Day Medical Specialized Laboratory in the Yazd city. Ten mL of venous blood was taken by a hemodialysis nurse before and at the end of the study. Samples were immediately transferred to an ice flask and then sent to the laboratory less than 30 minutes after being drawn. For serum separation, samples were centrifuged at room temperature up to 1500 rpm. After centrifugation, the samples were removed and frozen completely at -80°C. The samples of the first and second stages were tested simultaneously in a single day. Leptin and serum adiponectin levels were evaluated using enzyme-linked immunosorbent assay methods and the Diasourcekit (Belgium), Nediagnost kit (Germany), respectively. The patients' albumin and total iron-binding capacity levels were measured at the beginning of the study to assess patients' nutritional status.

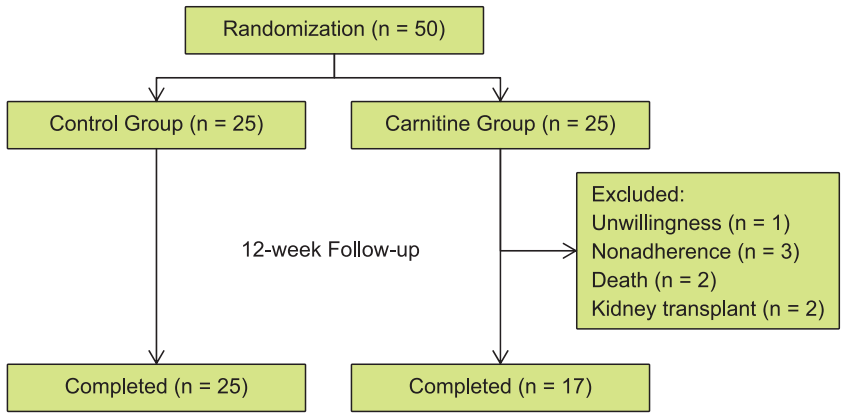
Statistical Analysis

Data analysis was performed using t the SPSS software (Statistical Package for the Social Sciences, version 16.0, SPSS Inc, Chicago, IL, USA). The chi-square test was used to compare qualitative variables between the two groups. Because all quantitative parameters had normal distribution according to the Kolmogorov-Smirnov test, the Student *t* test and the paired *t* test were used to compare parameters between and within groups, respectively. Results were expressed as mean ± standard deviation, and differences were considered significant if *P* value was less than .05.

RESULTS

Of 50 hemodialysis patients that were enrolled at the beginning of the study, 42 patients completed the study (Figure). The demographic characteristics of patients are reported in Table 1. There were no significant differences between the carnitine and the control groups in terms of age, duration of dialysis, sex, weight, BMI, diabetes mellitus, hypertension or dyslipidemia. Insignificant differences in the MIS values between the two groups at the beginning of the study showed a somewhat uniform distribution of the patients in terms of nutritional status in the two groups.

The outcome measures are shown in Table 2. A nonsignificant decrease was observed in the BMI of the control group. No difference was seen between the two groups in serum levels of leptin or adiponectin at the beginning of the study. After 12 weeks of L-carnitine supplementation, the mean of serum leptin was not significantly different between the two groups. The mean of serum leptin concentration was decreased in both groups, but not significantly in either group.



The recruitment flowchart of the study.

Table 1. Characteristics of Study Participants*

Characteristics	Carnitine Group (n = 17)	Control Group (n = 25)	*P*
Age, y	63.4 ± 12.9	62.1 ± 10.2	.72
Weight, kg	66.7 ± 14.0	65.9 ± 11.5	.86
Body mass index, kg/m^2	24.4 ± 3.4	24.6 ± 3.0	.82
Duration of dialysis, y	3.47 ± 2.35	3.35 ± 1.90	.86
MIS score	7.00 ± 2.96	6.96 ± 2.57	.69
Diabetes mellitus	12 (70.6)	15 (60.0)	.50
Hypertension	10 (58.8)	17 (68.0)	.50
Dyslipidemia	1 (5.9)	3 (12.0)	.50
Nutritional status			
Normal	8 (47.1)	16 (64.0)	
Intermediate	9 (52.9)	9 (36.0)	
Severe	0	0	.22

*Values are mean ± standard deviation or frequency (percent).

Table 2. Outcome Measures in Study Participants*

Outcome	Carnitine Group (n = 17)	Control Group (n = 25)	*P*
Body weight, kg			
Before	66.7 ± 13.9	65.8 ± 11.5	.80
After	66.7 ± 13.4	65.4 ± 11.9	.73
P for change	.90	.40	…
BMI, kg/m^2			
Before	24.4 ± 3.4	24.6 ± 3.0	.80
After	24.4 ± 3.3	24.4 ± 2.0	.99
P for change	.86	.31	…
Leptin, mg/dL			
Before	9.20 ± 12.96	15.97 ± 16.48	.16
After	7.40 ± 14.10	8.79 ± 13.14	.75
P for change	.67	.80	…
Adiponectin, µg/mL			
Before	8.6 ± 11.2	5.0 ± 2.5	.13
After	9.8 ± 4.1	11.2 ± 5.4	.39
P for change	.67	< .001	…

*Values are mean ± standard deviation.

The mean adiponectin concentrations were not significantly different between the two groups. At the end of the study, the mean of adiponectin concentration was increased in both groups; the change of adiponectin was not significant between the two groups.

DISCUSSION

This study showed that a daily intake of 1000 mg oral syrup of L-carnitine for 12 weeks did not affect leptin and adiponectin levels, weight, or and BMI in hemodialysis patients. L-carnitine supplementation has shown different results in different studies. Hussein and coworkers showed that L-carnitine supplementation significantly reduced high-fructose-diet-induced insulin resistance by reducing serum leptin level.[18] Nakazono and colleagues concluded that in patients on hemodialysis, the serum leptin concentration was a valuable clinical marker of the body fat content and could also contribute to the evaluation of hyperlipidemia.[19] Based on previous studies, adiponectin level of serum can be considered as an indicator of nutritional status in hemodialysis patients. Adiponectin changes during weight loss have been evaluated in several studies. Although it seems that adiponectin level is not affected by weight loss per se, its level has been changed differently by different treatments. Increase in adiponectin level has been observed by a low-calorie diet plus exercise as well as acetyl-L-carnitine supplementation. Elevated adiponectin serum levels could be explained by the hypothesis that an improved oxidation of free fatty acids might be associated with a secondary increase in adiponectin expression.[20]

In a clinical trial conducted by Shakeri and colleagues on 36 hemodialysis patients, L-carnitine supplementation through oral vials of 1 g daily for 12 weeks caused no changes in weight or BMI of patients compared with the control group.[13] Hakeshzedeh and coworkers demonstrated that the oral intake of 1 g of L-carnitine for 3 months had no effect on anthropometric indexes.[21] Ghazot and colleagues showed that injections of 15 mg/kg of body weight in hemodialysis patients caused no significant changes in patient weight compared with the control group[22]; the current study achieved similar results. In the current study,

there was no significant difference between the two groups in terms of average BMI at the beginning of intervention. Three months of intervention showed that a daily intake of 1 g oral carnitine supplementation had no effect on the BMI or weight of patients. Body mass index was decreased after 3 months in the control group, but this difference was not significant compared with the carnitine group. The study of Duranay and colleagues[23] and Savica and colleagues[24]showed that taking 20 mg/kg of intravenous L-carnitine caused a significant change in the BMI and weight of hemodialysis patients. In the study of Duranay, however, the difference in BMI between the two groups was significant at the beginning of the study. In these two studies, increased BMI was observed after 6 months of intravenous L-carnitine; these results are different than those of the current study. It seems that this difference in the studies can be due to medication type (intravenous versus oral) and dosage.

Leptin is a 16-kDa protein that regulates food intake and energy expenditure in animal models.[25] Expression and secretion of leptin is regulated by many factors. For example, leptin is increased under the influence of insulin, glucocorticoids, estrogen, and tumor necrosis factor-α, while it is decreased under the influence of androgen, free fatty acids, or growth hormones.[26,27] Data obtained from cross-sectional studies support the hypothesis that high levels of leptin play a role in anorexia and malnutrition.[28,29] A number of researchers have found no relationship between leptin levels and nutritional indexes.[30,31] The current study showed that 12 weeks of L-carnitine supplementation had no significant effect on serum leptin levels. The mean of serum leptin levels in both groups were decreased after 12 weeks, but this difference was not significant in any of the groups. Only one study has examined the effect of L-carnitine on serum levels of leptin. Csiky and associates showed that L-carnitine supplementation did not significantly change serum leptin levels; these results were in line with the current study.[16]

Adiponectin levels rise in CKD and hemodialysis patients. This fact shows that the kidney is an important factor in adiponectin renal clearance.[4,5] Kwan and Beddhu demonstrated the decreased expression of the adiponectin gene in patients with CKD.[6] However, other factors such as insulin resistance and energy protein malnutrition may also increase adiponectin levels in CKD patients.[32-34] Dervisoglu and colleagues showed that an increase in adiponectin levels is associated with a worse nutritional status and inflammation.[35] Zoccali and coworkers showed that adiponectin had an inverse relationship with risk factors of cardiovascular disease.[36] Lau and colleagues, in their review article, concluded that adiponectin has anti-inflammatory and insulin-sensitizing properties.[37-39] El-Shafey and colleagues also demonstrated that adiponectin was inversely associated with risk factors of cardiovascular disease and found that decreased levels of adiponectin were associated with insulin resistance and the prevalence of cardiovascular diseases in CKD patients.[5] Conversely, Tentolouris and colleagues concluded that adiponectin was a risk factor for cardiovascular disease.[40] The current study showed increasing the adiponectin levels in both groups, most significantly in the control group. In the carnitine group, however, there was no significant change. Statistical tests showed no change in serum adiponectin levels in the carnitine group compared with the control group. Few studies have examined the effect of L-carnitine on adipokines levels in hemodialysis patients. Only one study in this regard was found,[16] and its results showed that L-carnitine supplementation resulted in a significant increase in serum adiponectin levels. That study lacked a control group; however, and its results differed from those of the current study.

A general review of previous studies indicated that the present study is the second randomized controlled trial ever to examine the effects of L-carnitine supplementation on leptin and adiponectin levels in patients undergoing hemodialysis treatment. This study was done assuming that carnitine deficiency is common among hemodialysis patients, so blood carnitine levels were not measured before the study. Compared with similar studies, strengths of this study are the existence of a control group among patients and the patient nutritional status assessment by the MIS method.

This study was conducted assuming levels of leptin and adiponectin are impaired in hemodialysis patients. At the beginning of the study these adipokines levels were not compared with those of healthy subjects. The other limitations of present

trial were the lack of measurement of serum carnitine concentration and dietary intake of it. Not taking food records of patients is another weakness of this study. It is also likely that adipokines contents in diabetic hemodialysis patients and hemodialysis patients without diabetes mellitus were different. Similar studies about the effect of oral L-carnitine supplementation on serum leptin and adiponectin concentration were very few. Further clinical trials are recommended.

CONCLUSIONS

This study showed that a daily supplementation of 1000 mg of oral L-carnitine syrup for 12 weeks did not affect on the serum leptin and adiponectin levels or weight or BMI of hemodialysis patients.

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CONFLICT OF INTEREST

None declared.

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